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**Serial No. :** *10/534,116*

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**Title :** *New Phenyl-naphthalene compounds*

**Art. Unit. :** *1626*

**Examiner :** *S. YOUNG*

***HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS***  
***WASHINGTON, D.C 20231***

**Declaration under 37 CFR 1.132**

I, Philippe DELAGRANGE, a citizen of France, of 23, rue Victor Hugo, 92130 Issy les Moulineaux, France, declare and say that :

I hold the degree of Doctor of University from the University Pierre et Marie Curie of Paris in 1990. In 1991, I was appointed as Scientific Study Manager in Servier International Research Institute and Head of Pharmacological Projects in 1995 in Melatonin field.

I am the author or co-author of 35 patents and 130 international publications, the majority of which are devoted to the melatonin pharmacology.

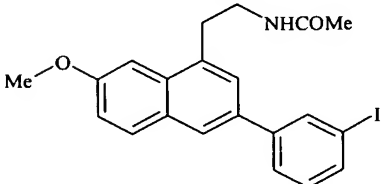
I am one of the co-inventors of U.S. Patent Application serial No. 10/534,116 filed May 5, 2005 concerning "New Phenyl-naphthalene compounds".

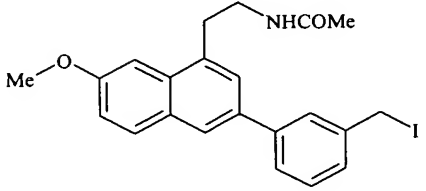
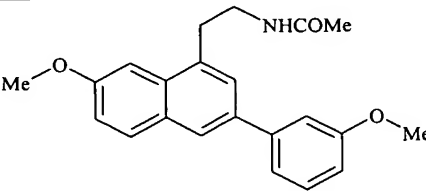
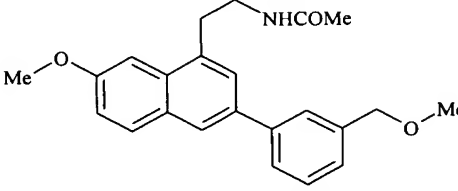
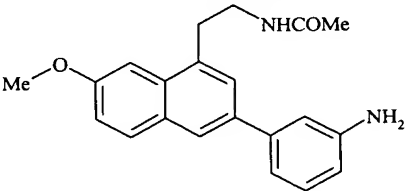
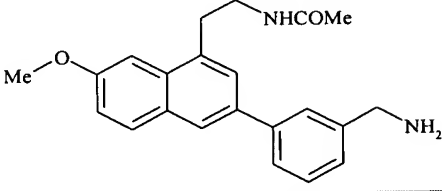
I am thoroughly familiar with the above-mentioned patent application and fully support the pharmacological experiments contained therein which were performed either by me or under my supervision. I also fully support the conclusions derived and the arguments presented as concerns the potential therapeutic interest of the compounds described.

The purpose of the present invention is to provide compounds having an activity on the melatonin receptors. The melatonin receptors are known to be divided in subtypes and the compounds of the invention have a very good melatonin receptor binding affinity. Because of this affinity, the compounds of the present invention are candidates for the treatment of disorders in which melatoninergetic system is involved.

In the field of the melatoninergetic ligands, lots of compounds have been synthesized, with different structures. The requirements of the drugs authorities encourage the finding of new compounds with a great efficacy, a better selectivity when different subtypes of receptors exist, and a better stability in humans. This last point is very important in the melatoninergetic field as lots of melatoninergetic ligands have a poor stability : the consequences are a high degree of variability from one to another human, a bad predictability of toxicity as much more metabolites can be present, and a lost of control of the activity of the compound.

However, it is difficult and topical to try to synthesize compounds bearing a selectivity for one or the other receptor subtypes and/or a better bioavailability in human, this parameter being very often low in that field. Some comparisons have been done using those two parameters (selectivity and bioavailability) between compounds of the prior art and Examples of the present invention. The results obtained are presented in the following table :

<p><b><i>Prior Art US 6,143,789</i></b>  <b><i>Example 11</i></b></p>		<p>Selectivity MT<sub>1</sub>/MT<sub>2</sub> = 87</p>
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<b>Example 5</b>		Selectivity MT <sub>1</sub> /MT <sub>2</sub> = <b>178</b>
<b>Prior Art US 6,143,789 Example 13</b>		Selectivity MT <sub>1</sub> /MT <sub>2</sub> = <b>23</b>
<b>Example 6</b>		Selectivity MT <sub>1</sub> /MT <sub>2</sub> = <b>216</b>
<b>Prior Art US 6,143,789 Example 26</b>		Metabolic Stability in Human : <b>10 %</b>
<b>Example 7</b>		Metabolic Stability in Human : <b>80 %</b>

In the light of the above references, it is clear that a high affinity and/or selectivity for the melatonergic receptors is definitely and positively linked to their utility in the treatment of the pathologies included in our demand.

The results obtained for the affinity of the compounds are reinforced by the results obtained concerning the stability which is much better in our present application compared to the cited prior art. This allows to think that not only we have very powerful compounds but also that it will be possible to reduce the variability inter individual.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further declarant sayeth not

A handwritten signature in black ink, appearing to read 'P. Delagrangé', written over a horizontal line.

P. DELAGRANGE

Executed at : Courbevoie

Date : 03.06.04

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